Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-7, 9-10, 12-13, and 82-84 are pending in this application, with claim 1 being the independent claim. Claim 8 has been canceled without prejudice to or disclaimer of the subject matter therein. Claim 1 has been amended. It is believed these changes introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

Rejections for obviousness-type double patenting

Claims 1-10, 12, 13, and 82-84 were provisionally rejected on the basis of obviousness-type double patenting over claims 1-10, 19, 21, 22, and 24-25 of Appl. No. 10/766,528. Applicants request clarification of the rejection. There appears to be a typographical error in the Office Action (Paper No. 20060911), as the present application is Appl. No. 10/766,528.

If the Examiner meant to base the rejection on Appl. No. 10/851,637, then Applicants respectfully traverse the rejection in view of the recent cancellation of claims 1-42 in that application.

Rejections under 35 U.S.C. § 112, written description

Claims 1-10, 12, 13, and 82-84 were rejected for allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection and assert that the claims as currently presented have sufficient written description in the specification as originally filed.

Applicants note that the presently rejected claims were present in the application as originally filed, and that it has been long settled that "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). Applicants further note that originally filed claims are a part of the disclosure. 35 U.S.C. 112.

Applicants assert that the presently rejected claims define compounds by their interaction with a known substrate. The detailed disclosure of the wild type Gag substrate and of Gag mutants in paragraphs 46 and 53, SEQ ID NOS: 2-9, and figures 4-8 provide one of skill in the art distinguishing information that allows one to recognize the entire genus. The present case differs from the situation where an applicant "attempted to define an unknown by its binding affinity to another unknown." (*Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004)).

The MPEP, at 2163(II)(A)(3)(a), states that, "[a]n adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." (See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000)). Not only have

Applicants provided a number of compounds that function as maturation inhibitors, and detailed information about the compound's substrate, Applicants have also provided detailed procedures for testing a compound to determine its suitability as a maturation inhibitor at least in paragraphs 109-112.

Not only does the application as originally filed comprise sufficient written description for the pending claims, but also the application's specific content is buttressed by the documents incorporated by reference in the application as originally filed. Applicants note that pursuant to MPEP 2163.07(b), "[t]he information incorporated [by reference] is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed."

In addition to the number of betulin derivatives and dihydrobetulin derivatives disclosed in the specification as originally filed, a number of compounds that function as maturation inhibitors are disclosed in USPN 5,679,828, USPN 6,172,110, and in U.S. Patent Appl. Nos. 60/443,180 and 10/670,797. Furthermore, a number of oleanolic acid and promolic acid maturation inhibitors are disclosed in Kashiwada *et al.* (*J. Nat. Prod.* *61*:1090-1095 (1998)). Furthermore, a number of platanic acid maturation inhibitors are disclosed in Fujioka, T., *et al.* (*J. Nat. Prod.* *57*:243-247 (1994). Applicants believe that the compounds' incorporation by reference is sufficient to address the Examiner's concern; however, if the Examiner requires the chemical names and structures to be expressly included in the specification, Applicants will oblige and provide an amendment to the present specification. Replacing the identified material incorporated by reference with the actual text is not new matter.

As the present application contains sufficient written description, Applicants request that the 35 U.S.C. 112, 1st paragraph rejection be withdrawn.

Rejections under 35 U.S.C. 112, 1st paragraph, enablement

Claims 1-10, 12, 13, and 82-84 were rejected for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection and assert that the claims as currently presented are enabling to one of ordinary skill in the art.

Applicants will address the Wands factors in the order listed in the office action.

Nature of the Invention: Applicants agree with Examiner's statement that "[t]he claims are drawn to a method of treating HIV-1 infection in a patient, comprising administering a compound that selectively inhibits processing of the viral Gag p25 (CA-SP1) protein to p24 (CA)."

State of the Prior Art: Applicants disagree with Examiner's characterization of the state of the art, and additionally assert that whether a class of compounds is "routinely obtainable by those skilled in the art" is not the proper query to probe the state of the art. Firstly, as 3-O-(3',3'-dimethysuccinyl) betulinic acid, among other compounds, was disclosed as an HIV inhibitor in a patent application filed in 1995, the identity of a plurality of maturation inhibitors were "obtainable by those skilled in the art." Secondly, at least as early as 2004, the state of art for anti-retroviral therapy was quite advanced. The global scientific and medical community spent $6.1 billion dollars on the HIV epidemic in 2004. Moreover, approximately 1629 U.S. patents had issued by 2004 specifically addressing HIV therapeutics. While the majority of research efforts have been focused on protease and reverse transcriptase targets, a considerable background

knowledge base has been developed in HIV therapy over the last 25 years. Such an in-depth knowledge base allows one of skill in the art, upon reading the present disclosure, to instantly comprehend this invention. Given the extensive scientific, financial and political pressures to advance the state of anti-HIV therapy in 2004, coupled with the extensive disclosure of maturation inhibitors in the present application, Applicants believe that the Examiner should recognize the advanced state of the art in HIV therapeutics.

Breadth of Claims: The presently pending claims do not embrace treatment methods for all retroviruses expressing Gag, nor do they embrace treatment methods for all lentiviruses, nor do they even embrace all forms of HIV, rather the present claims are limited to HIV-1 therapy. Additionally, the adjacent amino acid residues relevant to Gag CA-SP1 cleavage are disclosed as being "about 15 residues on either side of the HIV-1 Gag CA-SP1 cleavage site" (specification, paragraph 71). Thus, the present claims are narrowly tailored, seeking only to embrace maturation inhibitors of specific criteria that interact with a well defined target protein and creating an effect no more than about 15 residues away from a pin-pointed cleavage site.

Working Examples: Applicants partially agree with Examiner's assertion that the application discloses inhibition in HeLa cells, but believe that the Examiner's characterization under appreciates the scope of the working examples. Example 1 discloses anti-viral activity in HIV-1 isolates in PBMC cells. Example 2 discloses anti-viral activity in HIV-1 isolates in MT-2 cells, wild type HIV-1 isolates, and isolates comprising resistance-conferring mutations to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. Example 3

discloses anti-viral activity in HIV-1 isolates propagated in HeLa cells and MAGI cells. Example 5 discloses anti-viral activity in HIV-1 isolates propagated in H9 cells. Applicants assert that the disclosure of 5 cell types infected with either wild type or 1 of 7 drug resistant mutant viruses constitutes a broad range of working examples.

Guidance in the specification: Applicants disagree with Examiner's assertion that "the specification provides no guidance regarding practice of the claimed method." As discussed in Section A above, Applicants have provided a number of compounds that function as maturation inhibitors, detailed information about substrate identity, and detailed procedures for testing a compound to determine its suitability as a maturation inhibitor. Furthermore, the Examiner has not applied the proper test to evaluate the guidance provided by the specification. MPEP 2164.02 states that, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Those of skill in the art appreciate that in the case of a viral target, as opposed to a cellular target, in vitro results and in vivo results are strongly correlated. Other factors, including the highly conserved genetic sequence of Gag, and the claim element limiting treatment to HIV-1 (rather than all viral Gag proteins) make the correlation even stronger. Quoting further from MPEP 2164.02, Applicants note that, "the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example" and that, a "rigorous or an invariable exact correlation is not required." As the present application provides considerable guidance respecting active compounds, substrate identity, and detailed testing procedures, Applicants request the Examiner to reevaluate the thoroughness of guidance provided in the specification.

Predictability in the art: The Examiner's characterization of the predictability in the art focuses on "drug resistance," "minority HIV-1 variants," and "Darwinian selective pressures." Applicants certainly appreciate the Examiner's concerns; in fact, one factor motivating Applicants to develop maturation inhibitors is the fact that drugs that interact with a novel target are expected to be active against viruses harboring resistance-conferring mutations (see table 4 of the present application). None of the mutations that confer resistance to currently marketed drugs affect the activity of maturation inhibitors. Further, applicants note that no clinical HIV-1 isolate harboring a mutation to maturation inhibitors has been identified despite intensive efforts to identify one. Since maturation inhibitors, which interact with a novel viral target, do not exhibit reduced activity against mutant viruses that are resistant to other drugs, Applicants respectfully request Examiner to reconsider her position on the predictability in the anti-HIV art.

Amount of experimentation necessary: Applicants disagree with Examiner's characterization of the amount of experimentation necessary, and additionally assert that working examples regarding clinical efficacy in humans, therapeutic index and pharmacokinetic properties of maturation inhibitors are not, and never have been, part of a patentability inquiry. Rather, those properties are the bailiwick of the FDA, and it is the FDA that has the expertise to evaluate such properties. The present application discloses methods and results for identifying maturation inhibitors by methods known to those of skill in the art, including: p25 cleavage endpoint (Example 1), XTT endpoint (Example 2), galactosidase indicators (Example 3), and EM microscopy (Example 6, Figure 3). As indicated above, the present application discloses a number of compounds that function

as maturation inhibitors, detailed information about substrate identity, and several detailed procedures for testing a compound to determine its suitability as a maturation inhibitor. Given the Applicants' extensive disclosure, the amount of experimentation necessary to practice the present invention can not be characterized as an unduly burdensome.

As the present application is enabling to one of skill in the art, Applicants request that the 35 U.S.C. 112, 1st paragraph rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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